REMARKS

Upon entry of the instant amendment, claims 35-64 are pending. Claims 23-34 have been cancelled without prejudice or disclaimer and claims 35-64 have been added. Support for the new claims is found throughout the specification as filed, for example, at page 5, first paragraph to page 8, first paragraph; and the claims as originally filed. The fact that claims 23-34 have been canceled is not to be construed an admission by Applicant or Applicant's agent that such claims are not patentable, and Applicant reserves the right to pursue the subject matter of the canceled claims in a divisional or continuing application.

No new matter has been added by way of amendment.

I. Election/Restriction

Applicant acknowledges that the Examiner has withdrawn claims 26, 30 and 34 from consideration. Applicant respectfully points out that these withdrawn claims have been canceled and that new claims 59-64 have been added which are directed to methods of preventing RSV infection. If the Examiner also withdraws these claims, Applicant respectfully requests that the Examiner rejoin claims 59-64 pursuant to MPEP § 821.04 in the event the independent claims from which they depend are allowed.

II. Rejections Under 35 U.S.C. § 103 (a)

A. Claim 23-25, 26-29, and 31-33 stand rejected under 35 U.S.C. § 103 (a) as allegedly being unpatentable over Jones *et al.* in view of Beeler *et al.* In particular, the Examiner asserts at page 7 of the Office Action:

> [o]ne of ordinary skill in the art at the time of invention knowing that the CDR regions of murine antibodies can be grafted into human antibodies would have been able to take the murine monoclonal antibodies of Beeler *et al.* and modify them as taught by Jones *et al.* with the expectation of success in creating an antibody that is an anti-RSV F neutralizing monoclonal antibody that binds to the antigenic site A or C. Jones *et al.* provides the motivation and expectation of success to make [an] anti-RSV-F human-murine monoclonal antibody because Jones *et al.* was able to make a human-murine monoclonal antibody with CDRs from a murine antibody antibody.

Applicant respectfully disagrees and traverses this rejection.

Applicant respectfully points out that to find obviousness, there must be a reason or suggestion in the art for carrying out the invention other than the knowledge learned from the Applicant's disclosure. *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). The proper inquiry is whether the art suggested the invention at the time the invention was made, and whether the art would have provided one of ordinary skill in the art with a reasonable expectation of success. *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be found in the prior art and not in the Applicant's disclosure. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991) (emphasis added).

Preliminarily, Applicant respectfully points out that, in order to expedite prosecution of the application, Applicant has cancelled claims 23-34 and added new claims 35-64. Specifically, independent claims 35, 43 and 47 recite "...protects cotton rats against lower respiratory tract infections caused by RSV when administered to cotton rats" and independent claims 39, 51 and 55 recite "...protects humans against lower respiratory tract infections caused by RSV when administered to humans."

Applicant respectfully points out that even assuming *arguendo* that the combination of the teachings of Beeler *et al.* and Jones *et al.* renders certain RSV antibodies against the A or C site of the F protein obvious (with which Applicant disagrees, *see* response dated Jan. 12, 2004), these teachings (alone or in combination) certainly do not render obvious antibody compositions comprising human-murine RSV antibodies against the A or C site of the F protein that are protective in animals, for example, in cotton rats or humans.

Applicant respectfully asserts that the Examiner cannot reasonably conclude that the teachings of Beeler *et al.* and Jones *et al.* render the claimed protective antibody compositions obvious without using improper hindsight reasoning. Prior to the invention of the claimed antibody compositions, one skilled in the art simply would not reasonably conclude which, if any, of the 18 mouse antibodies disclosed in Beeler *et al.* having *in vitro* neutralization activity would be protective in an *in vivo* model (such as humans or cotton rats) whether or not they remained mouse antibodies or were "humanized" by artificially combining the teachings of Jones *et al.* For instance, as discussed in Walsh *et al.* (*J. Gen. Virol.* 1989, 70:2953-61, *see* Exhibit I; also cited as Information Disclosure Statement reference number 5), at the time of the present invention, it was well known in the art that *in vitro* neutralization of anti-RSV

monoclonal antibodies did not correlate well with *in vivo* protection (*see, e.g.,* abstract of Walsh *et al.*). In particular, Walsh *et al.* found that 25% (2 out of 8) antibodies that displayed *in vitro* neutralizing activity of the Long RSV strain did not confer protection in the cotton rat *in vivo* model. *See, e.g.,* page 2958, third paragraph; Figure 3a; and the abstract of Walsh *et al.* Protection in humans was not tested. Further, Walsh *et al.* tested a number of antibodies that were non-neutralizing *in vitro*, yet protective *in vivo* in the cotton rat model. Accordingly, Walsh *et al.* concluded that "[i]n this case, protection was not related to neutralizing capacity *in vitro* since a non-neutralizer (C14) also reduced lung virus titers." *See, e.g.,* page 2958, third paragraph of Walsh *et al.* Thus, one skilled in the art prior to the priority date of the instant application would not have viewed *in vitro* RSV neutralization activity of anti-RSV antibodies as a good and reliable indicator of *in vivo* protection. In fact, Applicant respectfully asserts that if one skilled in the art made human-murine antibodies from the Walsh *et al.* mouse antibodies, it would be even more unpredictable which, if any, antibodies would confer *in vivo* protection in humans.

Moreover, Applicant respectfully asserts that since Beeler *et al.* does not point out which, if any, of the 18 antibodies disclosed would be protective in animals, Beeler *et al.* fails to motivate one skilled in the art to "humanize" any particular antibody for further animal testing. This is underscored by the fact that the state of the art at the time (*see*, Walsh *et al.*) suggested that *in-vitro* RSV neutralization activity of anti-RSV antibodies is not a good and reliable indicator of *in-vivo* protection. The teachings of Jones *et al.* do not fill the gap left by Beeler *et al.* and motivate one skilled in the art to "humanize" any particular antibody to create the protective human-murine antibodies of the claimed invention. Moreover, even if it were obvious for one skilled in the art to try to use each of the Beeler *et al.* neutralizing mouse antibodies and other antibodies shown to have *in vitro* RSV neutralizing activity, "obvious to try" is not the legal standard under 35 U.S.C. § 103. The proper inquiry is whether the art suggested the invention at the time the invention was made, and whether the art would have provided one of ordinary skill in the art with a reasonable expectation of success. At best, Beeler *et al.* provided a number of mouse antibodies that bound RSV and had an *in vitro* effect just as Walsh *et al.* taught. To reach the conclusion that the invention was obvious based on the cited references alone, one would have to use improper hindsight reasoning. However, armed with the detailed teaching and data provided in the instant specification, one skilled in

the art would now reasonably conclude that Applicant has described and enabled protective human-murine antibody compositions wherein the antibody binds to the respiratory syncytial virus (RSV) F protein and wherein said antibody composition protects cotton rats and/or humans against RSV infections. Thus, in view of the foregoing, it would not have been obvious to a person skilled in the art to pick (or be motivated to pick) one or more of the Beeler *et al.* antibodies and reasonably expect to construct an antibody composition that is protective *in vivo* in cotton rats and/or humans. Therefore, Applicant respectfully request that the rejection under 35 U.S.C. § 103 be reconsidered and withdrawn.

B. Claims 23-25, 26-29, and 31-33 stand rejected under 35 U.S.C. § 103 (a) as being unpatentable over Queen *et al.* in view of Beeler *et al.* Specifically, the Examiner states at page 9 of the Office Action:

> [o]ne of ordinary skill in the art at the time of the invention would have been motivated to use the method of Queen *et al.* to make a human murine antibody directed against RSV using the CDRs of the murine monoclonal antibody of Beeler *et al.* knowing that Queen *et al.* teach success in making human-murine antibodies and knowing that Beeler *et al.* teach the importance of RSV and the neutralizing qualities of the murine monoclonal anti-RSV antibodies that they made.

Applicant respectfully disagree and traverse this rejection.

Preliminary, as pointed out above, Applicant has cancelled claims 23-34 and added new claims 35-64. Specifically, independent claims 35, 43 and 47 recite "...protects cotton rats against lower respiratory tract infections caused by RSV when administered to cotton rats" and independent claims 39, 51 and 55 recite "...protects humans against lower respiratory tract infections caused by RSV when administered to humans."

In addition, Applicant would like to comment on the Examiner's statement found at page 8 of the Office Action. Specifically, the Examiner states: "[a]s admitted by Applicant, Queen *et al.* teach how to make the inventive antibodies, but does not specifically disclose anti-RSV antibodies." Applicant respectfully assert that the Examiner has misconstrued the statements made by Applicant in the response and amendment submitted January 12, 2004. In

fact, Applicant did not admit that Queen *et al.* teach how to make the inventive antibodies of the present invention. Clarification is respectfully requested.

In response to the rejection, Applicant respectfully points out again that Beeler *et al.* does not disclose or suggest to one of ordinary skill in the art human-murine antibodies of any sort. More importantly, Beeler does not disclose or suggest to one of ordinary skill in the art which, if any, of the 18 murine monoclonal anti-RSV antibodies disclosed therein could be "humanized", retain viral neutralization properties, and be protective in animals. Contrary to the Examiner's assertions, Queen *et al.* does fill the void left by the Beeler *et al.* reference.

Applicant respectfully assert that, the Examiner cannot reasonably conclude that the teachings of Beeler *et al.* and Queen *et al.* render the claimed protective antibodies obvious without using improper hindsight reasoning. As pointed out *supra*, prior to the invention of the claimed antibodies, one skilled in the art simply would not reasonably conclude which, if any, of the 18 mouse antibodies disclosed in Beeler *et al.* having *in vitro* neutralization activity would be protective in an *in vivo* model (such as humans or cotton rats) whether or not they remained mouse antibodies or were "humanized" using the teachings of Jones *et al.* For instance, as discussed in Walsh *et al.* at the time of the present invention, it was well known in the art that *in vitro* neutralization of anti-RSV monoclonal antibodies did not correlate well with *in vivo* protection (*see, e.g.,* abstract of Walsh *et al.*). In particular, Walsh *et al.* found that 25% (2 out of 8) antibodies that displayed *in vitro* neutralizing activity of the Long RSV strain did not confer protection in the cotton rat *in vivo* model. *See, e.g.,* page 2958, third paragraph; Figure 3a; and the abstract of Walsh *et al.* Protection in humans was not assessed. Further, Walsh *et al.* tested a number of antibodies that were non-neutralizing *in vitro*, yet protective *in vivo* in the cotton rat model. Accordingly, Walsh *et al.* concluded that "[i]n this case, protection was not related to neutralizing capacity *in vitro* since a non-neutralizer (C14) also reduced lung virus titers." *See, e.g.,* page 2958, third paragraph of Walsh *et al.* Thus, one skilled in the art prior to the priority date of the instant application would not have viewed *in vitro* RSV neutralization activity of anti-RSV antibodies as a good and reliable indicator of *in vivo* protection. In fact, Applicant respectfully asserts that if one skilled in the art made human-murine antibodies from the Walsh *et al.* mouse antibodies, it would be even more unpredictable which, if any, antibodies would confer *in vivo* protection.

Thus, at best, Beeler *et al.* provided a number of mouse antibodies that bound RSV and had an *in vitro* effect just as Walsh *et al.* taught. Queen *et al.* relates generally to "humanized" antibodies, but Queen *et al.* does not disclose anti-RSV antibodies, much less, antibodies that would be protective against RSV in vivo. The combination of these two references does not motivate the skilled artisan to pick any particular RSV antibody to "humanize," nor do the references allow the skilled artisan to reasonably conclude that one could make a human-murine RSV antibody which would be protective in humans and/or other animals. To reach the conclusion that the claimed invention was obvious based on the cited references alone, one would have to use improper hindsight reasoning. However, armed with the detailed teaching and data provided in the instant specification, one skilled in the art would now reasonably conclude that the Applicant has described and enabled protective human-murine antibody compositions wherein the antibody in said composition binds to the respiratory syncytial virus (RSV) F protein and wherein said antibody composition protects cotton rats and humans against RSV infections. Therefore, for the above stated reasons, Applicant respectfully requests that the rejection under 35 U.S.C. § 103 be reconsidered and withdrawn.

III. Commercial success

Applicant respectfully points out, assuming *arguendo* that the Examiner has established a *prima facie* showing of obviousness of the pending claims, Applicant has presented in the response dated January 12, 2004 overwhelming evidence that an embodiment of the claimed invention, Synagis®, has achieved commercial success and satisfied a long felt need. *See*, Exhibits 1-5 submitted January 12, 2004; and pages 10-12 of the response. In concluding that Applicant's Exhibits and reasoning was not persuasive, the Examiner asserts at page 8 of the instant Office Action:

> First, the claims under consideration are not drawn to methods of preventing, so the argument is not commensurate with the scope of the claim.
> Second, the exhibits are not supportive of the full scope of the presently claimed antibodies. The exhibits are not persuasive because they are drawn to one product and the claims are drawn to a whole genus, see MPEP 116.03(a).

Applicant respectfully traverses this reasoning.

For commercial success of a product embodying a claimed invention to have true relevance to the issue of nonobviousness, that success must be shown to have in *some way been due* to the nature of the claimed invention, as opposed to other economic and commercial factors unrelated to the technical quality of the patented subject matter. *Cable Elec. Prod., Inc. v. Genmark, Inc.*, 770 F.2d 1015, 1027 (emphasis added). Therefore, the proper test is whether success has been shown to have in *some way been due* to the nature of the claimed invention and related to the technical quality of the patented subject matter. *Cable Elec. Prod., Inc. v. Genmark, Inc.*, 770 F.2d 1015, 1027 (emphasis added).

Accordingly, Applicant respectfully points out that the evidence and the arguments presented in Applicant's response filed January 12, 2004 establishes that an embodiment of the claimed invention (*e.g.,* of canceled claims 23-26 and new claims 35, 39, 44, and 52), Synagis®, does in fact bind the RSV F protein (*see* Exhibit 1, first paragraph, submitted January 12, 2004) and is protective in both the cotton rat *in vivo* model and in humans. *See*, Exhibit 4 (*e.g.,* abstract) and Exhibit 5 (*e.g.,* at page 203), both submitted January 12, 2004. In addition, Applicant respectfully points out the significant commercial success of the Synagis® murine-human antibody composition is connected "in some way" to the fact that the Synagis® antibody binds RSV F protein and is protective in animals. It is this particular functional property specified in the instant claims that contributes to the commercial success of Synagis®. Therefore, the success of the product is due the technical nature of the rejected claims.

Moreover, the Examiner has not provided any authority as to why claims drawn to a genus cannot be supported by the commercial success of a species of the claimed invention. Applicant is not aware of any such authority.

In view of the foregoing, assuming *arguendo* that the Examiner has established a *prima facie* showing of obviousness of the pending claims, the Applicant has presented overwhelming evidence that the claimed invention as embodied by Synagis® has achieved commercial success and satisfied a long felt need. Thus, Applicant has successfully rebutted a *prima facie* showing of obviousness. For the above-stated reasons, Applicant respectfully requested that the rejection under 35 U.S.C. § 103 be reconsidered and withdrawn.

CONCLUSION

Applicant believes that this application is in condition for allowance, and it is therefore respectfully request that a favorable action be granted.

Respectfully submitted,

Date: 10/19/04

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~~Edward~~ Amaya (Reg. No.)
Agent for the Applicant

MedImmune, Inc.
One MedImmune Way
Gaithersburg, MD 20878
Telephone: 301-398-4129